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REVIEW ARTICLE

Maintenance of Fertility in Patients With Rheumatic Diseases Needing Antiinflammatory and Immunosuppressive Drugs

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Introduction

The recently expanded understanding of the genetic and immunopathologic mechanisms of rheumatic diseases could result in improved, targeted therapies and a better prognosis. Because patients are living longer, improving quality of life has received more clinical attention. Regarding reproduction, both adult patients and adolescents often have concerns about their fertility (1–4).

Fertility is the ability to have a child and fecundity is the time to achieving pregnancy (5). Gonadal dysfunction and infertility in patients of both sexes with chronic rheumatic illness are multifactorial (1,5). Impaired health status, such as malnutrition, obesity, alcohol, tobacco or illicit drug use, and female and male genital disorders (6), may reduce fertility (1,5). Furthermore, hypothalamic–pituitary–adrenal axis dysfunction (2–4); autoimmunity with production of anti–corpus luteum, antiendometrial (1), or antisperm antibodies (3,4); high disease activity or chronic renal failure (1); and immunosuppressive drugs (7,8) can induce impairment of fertility in patients with rheumatic diseases.

Of note, in the healthy population, the reproductive capacity declines with increasing age in both sexes (6). In addition, in adults and adolescents with autoimmune diseases such as systemic lupus erythematosus (SLE) (1) and juvenile idiopathic arthritis (JIA), the fertile period may be shortened due to premature ovarian failure (POF) with menopause before age 40 years and high levels of follicle-stimulating hormone (FSH) (1,2).

Importantly, the main contributing factor for gonadal dysfunction and infertility in female and male patients with rheumatic diseases seems to be drug therapy (7–9). The effects of nonsteroidal antiinflammatory drugs (NSAIDs), immunosuppressive drugs, and biologic agents on male and female fertility are shown in Table 1.

Some drugs can cause reversible infertility, such as NSAIDs in women (10–13) and sulfasalazine (14–17) in men. Sperm abnormalities may occur in rare cases with methotrexate (18,19). Irreversible infertility in both sexes is observed exclusively after treatment with alkylating agents, such as oral or intravenous (IV) cyclophosphamide (CYC) and chlorambucil (1,5). The use of chlorambucil has been reduced to few indications, such as amyloidosis in rheumatoid arthritis (RA) (20). CYC is still an indication for severe diseases, particularly SLE, vasculitis, idiopathic inflammatory myopathies, and scleroderma, with a low cost and good adherence to treatment. Because, to our knowledge, no review on maintenance of fertility in pre- and postpubertal patients of both sexes during therapy with NSAIDs and/or immunosuppressive drugs exists, we undertook a review of the English-language literature.

Biologic agents are not included in this review because there is no convincing evidence of serious gonadal dysfunction induced by these drugs. In fact, there are numerous reports of new pregnancies inadvertently occurring during therapy with adalimumab, etanercept, and infliximab, and experts suggest that tumor necrosis factor α (TNFα) inhibitors may be continued during pregnancy when strongly indicated (9). Whether abatacept and rituximab exert harmful effects on reproduction has not been studied, although several pregnancies have occurred under treatment with rituximab (9). Semen abnormalities have rarely been studied in patients with rheumatic diseases treated with biologic agents, but the available data suggest that semen quality is relatively preserved. The decreased sperm motility and the reduced number of normal oval forms observed in 8 men with inflammatory bowel disease treated with infliximab was present before

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Table 1. Effect of NSAIDs, immunosuppressive drugs, and biologic agents on male and female fertility*

Drug	Effect
NSAIDs	
Females	May inhibit ovulation
Males	No influence on spermatogenesis
Chloroquine, hydroxychloroquine	Does not impair fertility in males or females
Sulfasalazine	
Females	No influence on fertility
Males	Reversible oligospermia, asthenozoospermia, and teratozoospermia Stop 3 months before planning a pregnancy
Cyclophosphamide	
Females	Risk of infertility related to cumulative dose and age Protect ovarian function by treatment with a GRH analog
Males	Risk of infertility related to cumulative dose Cryopreservation of sperm necessary before treatment
Methotrexate	
Females	No influence on fertility
Males	Reversible impairment of spermatogenesis possible Stop 3 months before planning a pregnancy
Leflunomide	
Females	No influence on fertility Perform washout before planning pregnancy
Males	Few data; no influence on male fertility
Mycophenolate mofetil	Does not impair fertility in males or females
Azathioprine	Does not impair fertility in males or females
Cyclosporin	Does not impair fertility in males or females
TNFα blocker	
Females	No influence on fertility
Males	No influence on spermatogenesis or fertility

* NSAIDs = nonsteroidal antiinflammatory drugs; GRH = gonadotropin-releasing hormone; TNFα = tumor necrosis factor α.

treatment, and therefore the drug cannot account for this finding (21). A mild semen abnormality was shown in 2 of 3 ankylosing spondylitis patients receiving anti-TNFα inhibitors (22), contrasting with a recent report of 4 ankylosing spondylitis patients who had 6 healthy children during infliximab therapy (23).

Materials and Methods

Literature search. We performed a computer-assisted (Medline; National Library of Medicine) search of the literature from 1966 to 2009 using the following terms: fertility, gonadal toxicity, rheumatic diseases, NSAIDs, and immunosuppressive drugs. Seventy-eight articles were selected for this review: original articles, case reports, or letters to the editor (n = 51); reviews (n = 25); and meta-analyses (n = 2).

Female sex

Assessment of female fertility in clinical practice. In contrast to the testicular tissues, where spermatozoa are constantly produced, the ovarian function depends largely on primordial follicles that are successively lost during the fertile period of life. Females have approximately 6–7 million primordial follicles at birth, and the number decreases to 500,000 at the beginning of puberty. One thousand primordial follicles are recruited during a menstrual cycle; however, often only one follicle reaches full maturity and ovulation, and the other primordial follicles undergo atresia (1). The normal menstrual cycle depends on the integrity of the hypothalamic–pituitary–ovarian axis based on pulsatile secretion of gonadotropin-releasing hormone (GRH), FSH, and luteinizing hormone (LH) (1,24).

The assessment of ovarian function (Table 2) is extremely complex and no single test is accurate to predict ovulation (1). Analysis of the menstrual cycle, pelvic ultrasound, and hormone profiles is necessary for assessment of ovarian function (2). Serologic parameters of ovarian reserve include FSH, LH, and estradiol measured at the follicular phase on days 1–3 of the menstrual cycle, and progesterone measured at the luteal phase 7 days before the next menstruation to confirm ovulation (1,2). Other markers of ovarian function include static tests, such as serum inhibin B and anti-Müllerian hormones, and dynamic tests, such as the clomiphene citrate challenge test, GRH agonist–stimulating test, and exogenous FSH ovarian reserve test. The serum anti-Müllerian hormone is produced by granulosa cells of the recruited follicles and is

Table 2. Assessment of female and male gonadal functioning in clinical practice*

Evaluation of gonadal functioning
  Female
    1. Tanner stage, age of menarche, and menstrual cycle
    2. Gynecologic examination
    3. Ovarian function in regular menses
      FSH, LH, and estradiol (on days 1–3 of the menstrual cycle)
      Progesterone (7 days before the next menstruation)
    4. Hormones in irregular menses
      Prolactin
      Thyroid function and testosterone (signs and symptoms of hyperandrogenism)
    5. Pelvis ultrasound (ovarian volumes and antral follicle count)
    6. Other markers of ovarian function
      Serum inhibin B and anti-Müllerian hormones
      Dynamic tests (clomiphene citrate challenge test, GRH agonist–stimulating test, and exogenous FSH ovarian reserve test)
  Male
    1. Tanner stage and age of spermarche
    2. Urologic examination
    3. Testicular ultrasound
    4. Hormones
      FSH, LH, morning total testosterone, and inhibin B
    5. Semen analysis and antisperm antibodies

* FSH = follicle-stimulating hormone; LH = luteinizing hormone; GRH = gonadotropin-releasing hormone.

the only examination of ovarian function that can be measured in the follicular and luteal phases (25). It has shown great promise as a biomarker of ovarian reserve in SLE patients treated with alkylating agents (25,26).

Maintenance of fertility in women needing NSAIDs and immunosuppressive drugs. *Effects of NSAIDs on fertility in women.* NSAIDs are indicated for the treatment of pain, fever, and inflammation in rheumatic diseases. These drugs inhibit cyclooxygenase (COX), the enzyme that catalyzes the synthesis of prostaglandins. Prostaglandins are involved in ovulation and implantation (5,10), with increased concentrations in the fluid of the developing follicle in the preovulatory period. The enzyme expressed in preovulatory follicles and inducing the maturation of the ovum is COX-2. In rats and mice, inhibition of both COX-1 and COX-2 interferes with fertilization and implantation. Complete inhibition of COX-2 causes infertility in COX-1 knockout mice (27).

Studies in animals and humans have shown that NSAIDs can inhibit the rupture of the luteinized follicle, and thereby cause infertility (5). In a study of 13 women, of whom 6 received the selective COX-2 inhibitor rofecoxib, delayed follicle rupture was observed in 4 of them, but none had alterations of serum progesterone (12). A prospective and randomized trial of ibuprofen in 12 women showed a delay of 2 days or more in follicle rupture in 5 women (10). Likewise, 20 women treated with meloxicam and monitored for 4 menstrual cycles had a reversible delay of ovulation, with an increase in follicular size and a decrease in serum progesterone levels (13).

Several case reports and small series have shown transient infertility following treatment with indomethacin, diclofenac, piroxicam, and naproxen in women with rheumatic disease, resulting in the luteinized unruptured follicle syndrome (11). Women with RA and RA–lupus overlap conceived naturally after the discontinuation of NSAIDs for 5–6 months or achieved pregnancy due to in vitro fertilization (IVF) after 1–3 cycles (11).

Therefore, the prolonged use of NSAIDs is a relevant factor for infertility in women with rheumatic diseases (5,11). Of note, the majority of women with an inflammatory rheumatic disease treated with NSAIDs are not infertile, but extended studies are needed to evaluate the magnitude of risk in long-term users of NSAIDs and how to prevent anovulation. An alternative approach is dose reduction of the NSAID or transient withdrawal in the preovulatory phase, but the efficacy of this needs to be investigated.

Effects of alkylating agents on fertility in women. The most important alkylating agent used in female patients with rheumatic diseases is CYC. CYC reacts with DNA bases and damages the DNA repair mechanisms with consequent inhibition of cell replication and cell death. In the immature rat ovary, CYC reduced the number of ovarian granulosa cells and caused ovarian fibrosis (28). In humans, oral CYC or IV CYC impairs reproductive capacity due to ovarian primordial follicle damage, impairment of follicle maturation, follicle depletion (29), and eventual exhaustion (1). This damage is generally cumulative and irreversible, causing POF (1).

POF associated with therapy with CYC is related to the cumulative dose and age at onset of treatment (1,2). In women with cancer, the cumulative dose of CYC needed to induce amenorrhea was 20.4 gm at age 20 years, 9.3 gm at age 30 years, and 5.2 gm at age 40 years (30). The risk of permanent ovarian failure in SLE under CYC varies from 15% to 60% for all age groups (1). There is no safe threshold dose of CYC for irreversible amenorrhea, and it is not known whether patients who recover from amenorrhea will have early menopause (2). The risk of persistent amenorrhea is higher with daily oral treatment than with pulses of CYC (5).

Of note, prepubertal girls appear to be relatively protected from the gonadotoxic effects of CYC, but even adolescent females are at risk of ovarian injury (1,2). Importantly, there are two studies that evaluated ovarian functioning in adolescents with lupus (2,31). A retrospective study in the US showed that ovarian reserve was reduced in juvenile SLE patients treated with IV CYC compared with patients without this treatment (31). A Brazilian prospective study demonstrated that ovarian reserve was decreased in female SLE patients compared with healthy controls at the same pubertal stage, independent of IV CYC treatment (2). In both studies, none of the juvenile SLE patients had POF.

Maintenance of fertility in women needing alkylating agents. It is essential to preserve fertility with ovarian protection not only in postpubertal patients but also in prepubertal girls. In the postpubertal female, options for gonad preservation include hormonal contraceptives, GRH agonists, and embryo and oocyte cryopreservation. Ovarian tissue banking for future tissue transplantation is a preferable method for prepubertal girls. Future options include inhibitors of apoptose and GRH antagonist.

Hormonal contraceptives. A few case reports showed possible ovarian protection by use of hormonal oral contraceptives in women receiving chemotherapy for treatment of Hodgkin's disease (32). A subsequent large study with 121 females did not confirm ovarian function preservation by oral hormonal contraception in patients receiving high-dose alkylating chemotherapy (33). Moreover, there is no evidence that depot medroxyprogesterone acetate is efficient for ovarian protection in patients needing CYC (24). Large prospective studies will therefore be necessary before these therapies can be recommended for ovarian protection (34).

GRH agonists or analogs. Therapy with GRH agonists or analogs shows the most promising results for ovarian protection. They have been used in females with malignancies, IVF, endometriosis, dysfunctional uterine bleeding, and autoimmune diseases (35). The main commercial preparations of GRH agonists or analogs are leuprolide acetate, goserelin, nafarelin acetate (intranasal solution) (35), and triptorelin (decapeptyl pamoate) (1).

The possible mechanisms of ovarian protection with GRH agonists or analogs in patients receiving cytotoxic agents are induction of a quiescent or prepubertal gonadal state (35), reduction of ovarian perfusion with decreased exposure to CYC, ovarian GRH receptor modulation, upregulation of an ovarian protective molecule that may prevent follicular apoptosis (named sphingosine 1-phosphate), and protection of undifferentiated germ line cells (36).

Children with precocious puberty have been treated with GRH agonists or analogs to suppress gonadal function for several decades. The same approach seems to provide additional gonadal protection for pubertal girls treated with alkylating agents (1). However, GRH analogs or agonists did not induce ovarian preservation in prepubertal adolescents needing these therapies (35), nor in human male gonads (1).

The continuous use of GRH agonists or analogs induces an initial increase of gonadotropin levels (FSH and LH) and causes ovarian stimulation with a transient elevation of estrogen levels. Within 1–3 weeks of administration, a hypogonadotropic hypogonadism (low FSH, LH, and estradiol) is observed (37), resulting in medical castration (35). To ensure a complete ovarian suppression, the agonist should begin one to two weeks before the start of CYC treatment (24). However, in severe lupus nephritis, treatment with CYC sometimes needs to be started before the first dose of a GRH agonist. The GRH agonists or analogs inhibit the pituitary–gonadal axis and subsequently, the complete ovarian suppression reduces the rate of oocyte maturation (1). Women develop amenorrhea at 3–8 weeks of treatment with GRH agonists or analogs, and menses generally return 6–10 weeks after withdrawal of GRH agonists or analogs (35).

Ovarian protection with GRH agonists or analogs for 6 consecutive months during treatment with cytotoxic agents has been reported in only two studies in patients with autoimmune diseases, with promising results (38,39). The first study described 8 patients receiving alkylating agents with monthly intramuscular depot injection of GRH agonists or analogs compared with 9 untreated controls with connective tissue diseases. POF was not observed in women treated with GRH agonists or analogs compared with 5 of 9 untreated controls (38). The second study evaluated 20 SLE patients treated with monthly IV CYC and depot leuprolide acetate compared with 20 female historical controls matched by age and cumulative dose of CYC. POF developed in only one patient treated with GRH agonists or analogs versus 30% of controls (39).

A meta-analysis of ovarian protection by GRH agonists or analogs (triptorelin, leuprolide, or buserelin intranasally) during chemotherapy for autoimmune disease and hematologic malignancy was recently reported. A 68% increase in the rate of preserved ovarian function was observed in women under GRH agonist or analog treatment (relative risk [RR] 1.68, 95% confidence interval [95% CI] 1.34–2.1). Of note, more women treated with GRH agonists or analogs achieved pregnancy than those not receiving this therapy (RR 1.65, 95% CI 1.03–2.6) (40).

The main adverse events associated with GRH agonist or analog therapy are injection site reactions (3–8%), unless a nasal GRH agonist or analog spray is used, and hypoestrogenism (hot flash, dry vagina, and irregular vaginal bleeding) (1). These menopausal symptoms disappear generally 6–10 weeks after GRH agonist or analog withdrawal (35). Loss of bone density by decrease of estrogen (1) is, however, the most serious side effect. The underlying chronic inflammatory disease and the high frequency of long-term glucocorticoid therapy also contribute to osteoporosis (35). Concomitant calcium and vitamin D supplementation (35), bisphosphonate therapy (1), or transdermal estrogen supplementation (39) are therefore necessary. Reversible loss of bone mineralization during GRH agonist or analog therapy seems to be less prominent in children than adults. To minimize bone loss, GRH agonists or analogs are generally administrated for no longer than 6 consecutive months (1). Seizures were reported in some patients with GRH agonist or analog therapy, and an association between GRH agonists or analogs and depression has been also described (1). Of note, GRH agonists or analogs were associated with the development of drug-induced SLE (41,42) and reversible thyroid dysfunction (1). Lupus flares may be induced by the increase of estrogen that is observed in the first two weeks of the start of GRH agonist or analog therapy (1), with a few cases of SLE activity triggered by this drug, including one fatal outcome (43,44). Anticoagulation in patients with SLE and/or the antiphospholipid syndrome for the first 3 weeks of GRH agonist or analog treatment seems prudent.

The efficacy and safety of GRH agonist or analog therapy in women of childbearing years and adolescent females with rheumatic diseases remain to be determined. Two ongoing studies in young women with SLE, PREGO (prospective randomized study on protection against gonadal toxicity) (45) and a randomized placebo-controlled trial to investigate the best dose regimens of triptorelin before CYC therapy, may provide more accurate data regarding the efficacy of GRH agonists or analogs (1).

Embryo and oocyte cryopreservation. Another important aspect of preservation of fertility in patients receiving cytotoxic therapy is embryo and oocyte cryopreservation for future assisted reproductive technologies (ARTs) (34,46).

Only embryo cryopreservation for future IVF is an established method to preserve fertility in women with malignancies under chemotherapy (34,46). An immature oocyte (egg) is collected during a menstrual cycle, followed by in vitro maturation. Mature oocytes are inseminated by intracytoplasmic sperm injection and the embryo is cryopreserved (47). However, the method requires a delay of 15–30 days before the start of immunosuppressive treatment and a partner for sperm donation (34).

Oocytes can also be frozen and stored for future IVF (47). It is a preferable method for women without a partner, but has a low success rate of approximately 2% (43). Recently, embryo or oocyte cryopreservation prior to CYC therapy for future ARTs was described in 7 young women with autoimmune diseases. Interestingly, in lupus patients, immature oocytes were aspirated without previous gonadotropin ovarian induction due to the contraindication to hormonal stimulation (47). In fact, ovarian stimulation as a fertility treatment for ARTs in women with SLE has induced lupus flares, thrombosis (48,49), ovarian hyperstimulation syndrome, and multiple gestations (48), with adverse fetal outcome (29). Therefore, embryo or oocyte cryopreservation without hormonal stimulation seems to be promising.

Ovarian tissue banking for future autotransplantation. Other techniques for preserving fertility are applicable to children or prepubertal adolescents. Because ovarian tissue contains hundreds of small primordial follicles in younger females, the cryopreservation of ovarian tissue preferably removed as ovarian cortical strips by laparoscopic techniques for future autotransplantation is the preferred option (1,34). There are two cases of women with malignancies who had POF after chemotherapy. They had restoration of hormone production with recovery of the menstrual cycle and two successful pregnancies after autotransplantation of ovarian tissue (50,51).

Heterotopic transplantation of cryopreserved ovarian tissue is another option in females. Sites of transplants include abdominal walls and forearms (46). One woman had breast cancer and preservation of fertility before chemotherapy-induced menopause. Her ovarian function returned 3 months after heterotopic transplantation of cryopreserved ovarian tissue, her spontaneous menstrual cycles normalized after 6 months, and she conceived naturally after 2 months (52).

Other options. Other options for ovarian protection that require future studies include the GRH antagonist, with the advantage of not inducing the ovarian stimulation described in GRH agonist or analog treatment (53). This antagonist rapidly suppresses gonadotropin levels at the beginning of the treatment with an immediate normalization after withdrawal (36). However, in mouse models this medication did not protect the murine primordial follicle from the damaging effects of CYC (54).

In addition, cytotoxic agents can induce the apoptotic pathway, resulting in oocyte depletion and POF (34). Sphingosine 1-phosphate is an oocyte apoptotic inhibitor and protects ovarian function in doxorubicin-treated and irradiated female mice without damage to the offspring (55).

Male sex

Assessment of testicular function in clinical practice. The testicles are composed by seminiferous tubules and the interstitial region (1). The seminiferous tubules include germ cells (stem cells, spermatogonia, spermatocytes, and sperm) and Sertoli cells that produce inhibin B. The interstitial region is composed by Leydig's cells that produce testosterone (56). Sperm production in the testicles usually begins at approximately age 12–13 years, continues throughout life, and decreases with age (1).

The male gonadal function requires a global assessment that includes urologic clinical examination, testicular ultrasound, hormone profile, semen analysis, and evaluation of antisperm antibodies (1,3,4). The hormone profile should include initial determinations of FSH, LH, and morning total testosterone. For years, FSH has been the most important indicator of seminiferous epithelia function. Elevated levels indicate testicular damage (1,3). However, GRH, estradiol, and testosterone levels may directly affect FSH (57). Of note, inhibin B is produced almost exclusively by the testes' Sertoli cells in the seminiferous tubules and is a marker of testicular dysfunction. Inhibin B levels are lower in men with impaired gonadal function (4,57).

Maintenance of fertility in men treated with sulfasalazine or methotrexate. Sulfasalazine can induce spermatozoa abnormalities in rats (14), and oligozoospermia, asthenozoospermia, teratozoospermia, and infertility in men (5). These sperm abnormalities are caused by sulfapyridine, a metabolite of this drug (51), and oxidative stress (17), and folate supplementation does not prevent them. The hormonal status of men receiving therapy with sulfasalazine is normal. Spermatogenesis generally recovers approximately 2.5 months after stopping sulfasalazine therapy (8,14). In patients with ulcerative colitis, the therapy with enteric-coated mesalazine (5-aminosalicylic acid preparation) allows the recovery of sperm alterations induced by sulfasalazine (15).

Monotherapy with methotrexate does not, as a rule, induce infertility in men (8). Sperm abnormalities may occur in rare cases, as in a young man with severe psoriasis treated with methotrexate (5). Oligospermia was detected, but a normal sperm concentration was observed after the discontinuation of the drug (58). In a recent study, the administration of folic and folinic acid together with methotrexate therapy improved germ cell toxicity in mice (19).

In men, family planning must be discussed in the case of therapy with sulfasalazine and methotrexate. Contraception and sperm banking is not necessary in patients treated with sulfasalazine (8). Because of possible mutagenicity, methotrexate requires avoidance of pregnancy for the duration of treatment and 3 months thereafter. Some authors suggest sperm cryopreservation for patients receiving methotrexate, not because of gonadal dysfunction, but because of the unsettled question of mutagenicity (5).

Table 3. Strategies for maintenance of fertility and evidence levels in female and male patients needing alkylating agents*

	Efficacy and safety
Female	
1. Postpubertal	
Hormonal contraceptives	No efficacy (level C)
GRH agonist	Promising results (level A)
Embryo and oocyte cryopreservation	Promising results (level C)
GRH antagonist	Under investigation (level C)
Apoptotic inhibitors	Experimental
2. Prepubertal	
Ovarian tissue banking for future tissue transplantation	Rare cases of successful pregnancies after autotransplantation (level C)
Male	
1. Postpubertal	
Hormonal therapy	No efficacy (level C)
Sperm cryopreservation for future assisted reproductive technologies	Effective and safe (level C)
2. Prepubertal	
Cryopreservation of spermatogonial stem cells for future autologous intratesticular transplantation	Experimental

* Level C = consensus/expert opinion; GRH = gonadotropin-releasing hormone; level A = randomized controlled trial/meta-analysis; level B = well-designed, nonrandomized clinical trial (not shown) (79).

Maintenance of fertility in men needing alkylating agents. As described in women, the most important alkylating agent used in male patients with rheumatic diseases is CYC. This drug may induce depletion of germinal epithelium (3) and cause damage in Sertoli cells (4) and in Leydig's cells (58). Although the gonadotoxic effects of alkylating drugs depend on their mechanism of action, cumulative doses, and number of cycles (1,59), there is no safe threshold of the cumulative dose of CYC and it is not possible to predict which patients will become infertile (1,60). Sperm alterations according to the cumulative dose of CYC were described in two studies. A meta-analysis performed in children and adolescents treated with cytotoxic therapy (mainly CYC) for relapsing nephrotic syndrome showed a marked risk of semen abnormalities with cumulative doses of CYC greater than 300 mg/kg (7).

Sperm abnormalities were associated with IV CYC therapy in our patients with juvenile, young adult, and adult SLE (1,3). Recently, we also observed Sertoli cell dysfunction in SLE and demonstrated that the index inhibin B/FSH may be an early and useful marker of IV CYC toxicity in these patients (4). Semen alterations were also described in patients with RA and JIA patients with amyloidosis (61) and Behçet's disease (62) treated with CYC.

Although postpubertal adolescents are most vulnerable to permanent infertility with gonadotoxic therapy, testicular abnormalities could be present even before puberty (1). Some reports described an eventual recovery of sperm function after a duration of 1–6 years of CYC treatment for bone marrow transplantation (63,64).

Strategies for maintenance of fertility in postpubertal and prepubertal male patients needing alkylating agents are shown in Table 3. Cryopreservation of spermatogonial stem cells for future autologous intratesticular transplantation is a preferable method for prepubertal boys, whereas hormonal therapy and sperm cryopreservation for future ARTs are options for postpubertal males.

Hormonal gonad protection therapy. Regarding hormonal therapy for testicular preservation, a group of 15 men with nephrotic syndrome were treated with oral CYC in 5 men, IV CYC in 5 men, and IV CYC and testosterone in 5 men. Azoospermia was observed in all patients; however, after 6 months, normal sperm quality was observed only in patients treated with testosterone (65). However, other studies in patients with malignancies did not show a beneficial effect from hormonal treatment (56,66–69).

Sperm cryopreservation for future ARTs. Cryopreservation of semen and subsequent IVF is the only standard option currently available for postpubertal adolescents and adults prior to cytotoxic therapy (8,56,70,71). It is important to collect one or more sperm samples, even with low sperm count and motility, for future ARTs, particularly intracytoplasmic sperm injection (56). The procedure for young patients is often uncomfortable and may be more successful if unaccompanied by parents (1).

The eligibility criteria for semen banking in patients with cancer consist of age >12 years and Tanner stage 2 (early puberty). Adolescents need to understand the technique of masturbation and sign the informed consent (71). Other procedures for sperm collection in case of difficulties to masturbate (1) or with religious questions about masturbation (56) consist of electroejaculation (72), penile vibratory system (73), and testicular sperm aspiration (indicated in patients with azoospermia) (74).

A study evaluated the sperm quality of men with non-malignant systemic diseases, including 12 men with autoimmune diseases, before cytotoxic treatment. In spite of bad semen quality before sperm banking, spermatozoa of these patients may be adequate for future ARTs (70). Regarding the outcome of stored semen and future ARTs in

Table 4. General recommendations, gonadotropin-releasing hormone (GRH) agonist therapy, and sperm cryopreservation in cyclophosphamide-treated patients

Strategies
  General recommendations for cyclophosphamide therapy
    1. Smallest possible dose
    2. Alternative therapies: azathioprine or mycophenolate mofetil
  Female patients
    GRH agonist (leuprolide 3.75 mg intramuscular [IM] every 4 weeks, triptorelin 3.75 mg IM every 4 weeks, or buserelin 200 mg 3 times a day intranasal) (40)
      1. Begin 1–2 weeks before cyclophosphamide therapy
      2. Amenorrhea at 3–8 weeks of GRH agonist use
      3. Timing of GRH agonist treatment: 6 months
      4. Menses return 6–10 weeks after GRH agonist withdrawal
  Male patients
    Sperm cryopreservation
      1. Collect sperm sample before cyclophosphamide therapy: ≥1
      2. Semen collection by masturbation or invasive methods: penile vibration, testicular sperm aspiration, or electroejaculation
      3. Future intracytoplasmic sperm injection

cancer patients, 557 men had 749 semen samples cryopreserved. Approximately 10% of cancer survivors utilized their cryopreserved sperm, with 49% live births (75).

Freezing sperm is a safe method, and the incidence of abnormalities in the offspring of male cancer survivors conceived by natural means was not elevated (76). One barrier to this method is the elevated cost of specimen storage that may not be covered by the insurance company (77). If the patient dies or chooses not to have children, their semen samples can be destroyed (78).

Testicular tissue cryopreservation. Testicular biopsy with cryopreservation of spermatogonial stem cells for future autologous intratesticular transplantation is a preferable method for boys before puberty (56,68,78). This procedure has shown promising results in various animal models (78), but is still an experimental method that needs ethical approval and informed consent of patients and parents (56).

Strategies for maintenance of fertility and evidence levels (79) in female and male patients needing alkylating agents are shown in Table 3. General recommendations, GRH agonist or analog therapy, and sperm cryopreservation in CYC-treated patients are in Table 4.

Discussion

Reduced fertility is not uncommon in patients with rheumatic diseases. Reasons for impaired reproductive function are multifactorial, with drug treatment as the main factor for gonadal dysfunction. Some drugs can cause reversible infertility, such as NSAIDs in women and sulfasalazine in men. Irreversible infertility is observed exclusively after treatment with alkylating agents in both sexes.

Family planning must be discussed with all patients who need therapy with drugs that can cause transient or permanent infertility. In case alkylating agents are necessary, the lowest possible dose and alternative therapies, such as azathioprine or mycophenolate mofetil, must be considered. The rheumatologist should inform the patient about methods for preservation of fertility and refer the patient to a gynecologist or urologist for necessary assessments of gonadal function. The options for preservation of fertility will be different for prepubertal individuals of both sexes compared with options for postpubertal males and females. Therapy with a GRH agonist or analog or cryopreservation of embryos in postpubertal females and sperm cryopreservation for future ARTs in postpubertal males should be initiated before or at the start of treatment with CYC. The patients need to be informed of problems connected with preservation of fertility, such as side effects of GRH agonists or analogs, interventions still at an experimental stage or without proven success, and financial burdens. Experimental interventions always need ethical approval of the institution and informed consent of the patient.

Rheumatologists should ensure gonadal protection for all patients through counseling and assistance. A multidisciplinary team, including family members, should be involved in the decision making, but the main consideration is the desire of the patient.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Silva had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Silva.

Acquisition of data. Silva, Østensen.

Analysis and interpretation of data. Silva, Bonfa, Østensen.

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